



Tigerlily
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UNDERSTANDING GENETICS, BRCA AND PARP INHIBITORS

GUIDEBOOK

This guidebook is brought to you by:



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GENES:

Genes carry the information that determines which characteristics or features are passed on to you from your parents. These characteristics include eye color, blood type, and risks of getting certain diseases. Everyone inherits two sets of genes - one set of genes from your mother and one set of genes from your father, for a total of 20,000 and 25,000 genes. Most genes are the same in everyone, but less than 1% are slightly different between people. When there is a permanent change in the DNA sequence that makes up a gene, this is called a gene mutation. Only some gene mutations affect health and development.

GENETICS

Genetics is the study of genes or parts of genes that have a known function. Genetics looks at how characteristics are passed on from one generation to the next, and it can help you and your family learn about how conditions such as breast cancer are inherited, what screening and testing options are available, and what treatments are available.

GENETIC TESTING

Genetic testing is a type of medical test that examines your DNA to reveal changes in your genes that may cause illness or disease such as breast cancer. There are over 1,000 genetic tests in use, and more are being developed. Genetic testing is voluntary, and the results are confidential, like the rest of your medical record. The cost of testing ranges from \$300 to \$5000 depending on the complexity of the test. In many cases, health insurance plans will cover the costs of genetic testing when it is recommended by your doctor. The Affordable Care Act requires insurance plans that began on or after August 1, 2012 to cover genetic testing costs when the test is recommended by a provider. Further, if you have a BRCA1/2 gene mutation, the Affordable Care Act requires coverage of counseling to help you decide if taking medications to lower breast cancer risk is right for you. Health insurance providers have different policies about which tests are covered, so be sure to contact your insurance company beforehand to ask about coverage. You may also choose to pay out-of-pocket for the test if you are worried that the results of a genetic test can affect your insurance coverage. In this case, find out more about your state's privacy protection laws before asking your insurance company to cover the costs.





Typically, to perform the genetic test, a sample of your blood, saliva or other tissue is sent to a testing facility. Within a few weeks, the results are generally ready and provided in writing to your doctor or genetic counselor, or sometimes directly to you. After you receive your results, it is important that you speak with the your genetic counselor or healthcare professional to interpret the results and discuss health management options.

The results of genetic tests are not always straightforward, which often makes them challenging to interpret

and explain. Therefore, it is important for patients and their families to ask questions about the potential meaning of genetic test results both before and after the test is performed. When interpreting test results, healthcare professionals consider a person's medical history, family history, and the type of genetic test that was done. There are three types of results:

- **A positive test result** means that the laboratory found a change in a particular gene, chromosome, or protein of interest. Depending on the purpose of the test, this

GENOMICS IS A STUDY OF ALL OF THE GENES AND GENETICS IS THE STUDY OF SINGLE GENES.



result may confirm a diagnosis, indicate that a person is a carrier of a particular genetic mutation, identify an increased risk of developing a disease (such as cancer) in the future, or suggest a need for further testing. Because family members have some genetic material in common, a positive test result may also have implications for certain blood relatives of the person undergoing testing. It is important to note that a positive result of a predictive or presymptomatic genetic test usually cannot establish the exact risk of developing a disorder. Also, health professionals typically cannot use a positive test result to predict the course or severity of a condition.

- **A negative test result** means that the laboratory did not find a change in the gene, chromosome, or protein under consideration. This result can indicate that a person is not affected by a particular disorder, is not a carrier of a specific genetic mutation, or does not have an increased risk of developing a certain disease. It is possible, however, that the test missed a disease-causing genetic alteration because many tests cannot detect all genetic changes that can cause a particular disorder. Further testing may be required to confirm a negative result.
- **An uninformative, indeterminate, inconclusive, or ambiguous test result are as follows:** uninformative test results some-

times occur because everyone has common, natural variations in their DNA that do not affect health. If a genetic test finds a change in DNA that has not been associated with a disorder in other people, it can be difficult to tell whether it is a natural variation or a disease-causing mutation. An uninformative result cannot confirm or rule out a specific diagnosis, and it cannot indicate whether a person has an increased risk of developing a disorder. In some cases, testing other affected and unaffected family members can help clarify this type of result.

BENEFITS OF GENETIC TESTING

Genetic test results can provide a sense of relief from uncertainty and help you make informed decisions about managing your health care. For example, a negative result can eliminate the need for unnecessary checkups and screening tests in some cases. A positive result can direct you toward available prevention, monitoring, and treatment options. Some test results can also help you make decisions about having children.

RISKS OF GENETIC TESTING

The physical risks associated with most genetic tests are minimal, particularly if the test requires only a blood sample or cheek swab.

Emotional and social consequences of the test results are more common risks associated with genetic testing. When you receive your genetic test results and you are positive for a particular



genetic mutation, you may feel angry, depressed, anxious, or guilty. These results may create tension within a family because the results can reveal information about other family members in addition to the person who is tested. You may also worry that your genetic test results may cause you to experience genetic discrimination in employment or insurance.

LIMITATIONS OF GENETIC TESTING

Generally, the genetic test cannot determine if you will show symptoms of a disorder, how severe the symptoms will be, or whether the disorder will progress over time. Another major limitation of genetic testing is that there may not be a treatment strategy for that genetic disorder.

GENETIC DISCRIMINATION

Fear of discrimination is a common concern among people considering genetic testing. Genetic discrimination is how you would describe being

treated differently by your employer or insurance company because you have a gene mutation that causes or increases the risk of an inherited disorder. A federal law called the Genetic Information Nondiscrimination Act (GINA) is designed to protect people from this form of discrimination. GINA has two parts:

- **Title I prohibits genetic discrimination in health insurance.** This makes it illegal for health insurance providers to use or require genetic information to make decisions about your insurance eligibility or coverage. This part of the law went into effect on May 21, 2009.
- **Title II prohibits genetic discrimination in employment.** This makes it illegal for employers to use your genetic information when making decisions about hiring, promotion, and several other terms of employment. This



part of the law went into effect on November 21, 2009.

GINA and other laws do not protect people from genetic discrimination in all circumstances. For example, GINA does not apply when an employer has fewer than 15 employees. It does not cover people in the U.S. military or those receiving health benefits through the Veterans Health Administration or Indian Health Service. GINA also does not protect against genetic discrimination in forms of insurance other than health insurance, such as life, disability, or long-term care insurance.

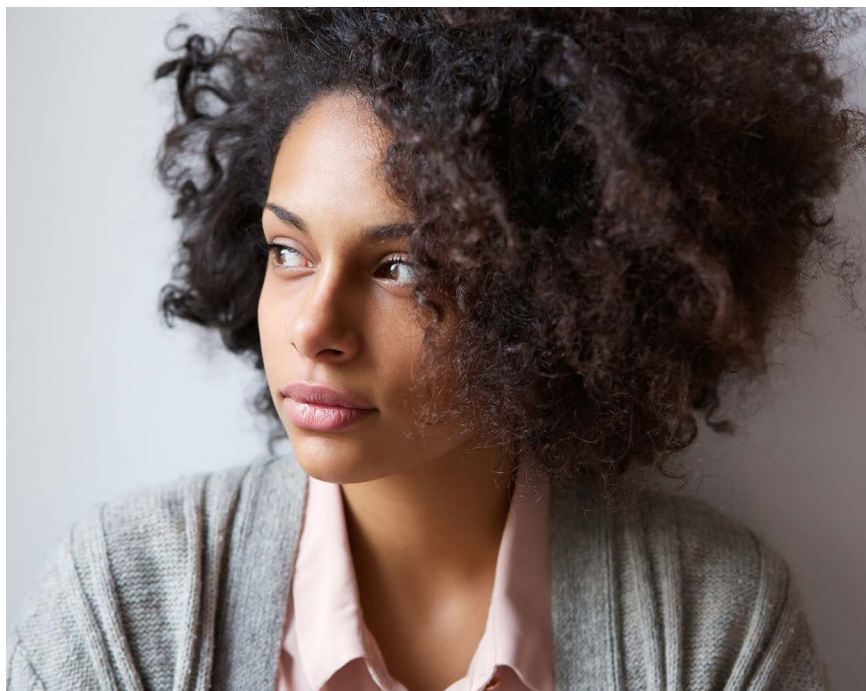
HEREDITARY BREAST CANCER

Hereditary breast cancer is a type of breast cancer that may be caused by a change in certain genes that you inherited from your mother or father.

These changes in the genes may prevent the genes from doing their job correctly. In turn, cells may divide and change more quickly, which can lead to cancer. Approximately 5%-10% of breast cancers are hereditary, which means that the cancer runs in the family.

BREAST CANCERS WITH BRCA GENE MUTATIONS

The normal BReast Cancer (BRCA) genes, BRCA1 and BRCA2, help to repair damaged DNA so that cells can continue to grow and function normally. Changes in the BRCA1 and BRCA2 genes increase the risk of breast cancer, and common mutants include BRCA1 185delAG, BRCA1 5382insC and BRCA 617delT. Here is some additional information about breast cancer with BRCA1/2 gene mutation:



- **Among Ashkenazi Jewish people**, approximately 1 in 40 have BRCA1/2 gene mutation.
- **Compared to breast cancers without a BRCA1** gene mutation or BRCA2 gene mutation, breast cancers that are associated with a BRCA1 gene mutation or BRCA2 gene mutation tend to be more common in younger women and tend to occur in both breasts.
- **BRCA1/2 gene mutation** may increase the risk of a second primary breast cancer, which means a second breast tumor that is unrelated to the first tumor. The second tumor typically occurs in the opposite breast, not the same breast. Women with BRCA1/2 gene mutation have a 10-30% chance of developing breast cancer in the opposite breast 10 years after diagnosis of the breast cancer. By comparison, women without BRCA1/2 gene mutations have 5-10% of developing breast cancer in the opposite breast 10 years after diagnosis of the breast cancer.
- **Mutations in BRCA1 gene and BRCA2** gene account for about 10% of all breast cancers, and this is considered to be rare. If you have a BRCA1 gene mutation or BRCA2 gene mutation or both, you may have approximately 40%-70% chance of being diagnosed with breast cancer. Therefore, not every woman who has a BRCA1 or BRCA2 gene mutation will get breast cancer. About 50 out of 100 women with a BRCA1 or BRCA2 gene mutation will get breast cancer by the time they turn 70 years old, compared to only 7 out of 100 women in the general United States population. Looking at each gene separately, those with mutations in BRCA1 gene have 55-65% chance of developing breast cancer by age 70; those with mutations in BRCA2 gene have 45% chance of developing breast cancer by age 70.
- **Mutations in BRCA1 gene and BRCA2** gene account for about 75-80% of hereditary breast cancers.
- **Women with BRCA1 gene mutation** have an increased risk of developing triple negative breast cancer. This type of breast cancer is estrogen receptor-negative, progesterone receptor-negative and HER2-negative.

WOMEN ARE AT HIGHER RISK OF BEING DIAGNOSED WITH BREAST CANCER THAN MEN. APPROXIMATELY 12% OF WOMEN GET BREAST CANCER AND 0.1% OF MEN GET BREAST CANCER.



- **Women with BRCA2 gene mutation** are more likely to have estrogen receptor-positive breast cancer.

GENETIC TESTING FOR BRCA GENE MUTATIONS:

To determine if genetic testing may be right for you, the best way to get started is to learn more about your family history on both your mother's and your father's side. An abnormal gene that increases breast cancer risk, such as BRCA1 or BRCA2 gene mutations, is more likely to run in your family if:

- **Three or more women** in your family have had breast and/or ovarian cancer, particularly if breast cancer is diagnosed at a younger age than this cancer typically develops (before age 50).
- **A close relative** has had cancer involving both breasts.
- **There is both breast and ovarian cancer** in your family.
- **Men in your family** have had breast cancer.
- **There is breast cancer** in your family and either male relatives on the same side of the family have had prostate cancer at a young age, or male or female relatives on the same side of the family have had other types of cancer, including but not limited to melanoma, pancreatic, stomach, uterine, thyroid, colon, and/or sarcoma.
- **Your family is of Ashkenazi** (Eastern European) Jewish descent.

To determine if you have BRCA gene mutations, your doctor or a genetic counselor may order testing for mutations in the genes individually or as part of a larger panel such as BRCA1, BRCA2, ATM, CDH1, CHEK2, PALB2, PTEN and TP53.





BRACANALYSIS CDx® AS GENETIC TEST FOR BRCA GENE MUTATIONS

There are many tests available for genetic testing. One of them is Myriad's BRACAnalysis CDx® is a genetic test that is approved by the FDA for detecting mutations in the BRCA1 and BRCA2 genes, which in turn determines if you are eligible for treatment with Poly (ADP-ribose) polymerase (PARP) inhibitors. This test can only be ordered by a qualified healthcare professional such as your doctor. To perform the test, a small amount of blood is drawn from you. Results usually take less than two weeks and are sent to

either the ordering healthcare provider or a designated "mail to" provider identified on the request form. The price of BRACAnalysis CDx testing is not made public. However, Myriad has published that the testing is covered by 97% of private insurance companies. Further, the average patient pays a coinsurance of less than \$54, and 75% of patients pay \$0.

If you are found to have an abnormal BRCA gene, you may proceed by testing the relative most closely related to you. If that next relative does not have it, you could not have passed it on to children. For example:

THE FACTORS THAT INCREASE YOUR CHANCES OF HAVING BREAST CANCER INCLUDE HAVING A PERSONAL HISTORY OF BREAST CANCER.

THERE ARE GENETIC TESTS AVAILABLE TO DETERMINE IF YOU HAVE MUTATIONS IN GENES THAT ARE ASSOCIATED WITH INCREASED RISK OF DEVELOPING BREAST CANCER.

- **If your mother's sister has an abnormal BRCA gene**, the next person to be tested would be your mother. If your mother's test is negative (no gene abnormality present), then you do not need to be tested, because she could not have passed the mutation on to you. If your mother's test is positive, you might then decide to be tested. If your mother is no longer living, then you might go ahead with testing on the basis of your aunt's test result.
- **If you test positive for an abnormal BRCA gene**, the next people to be tested would be your siblings and/or your adult children. If any of them test positive, then they could have passed the mutation on to their own children. If they test negative, then they could not have passed on the mutation.

PARP INHIBITORS

PARP proteins normally help repair damaged DNA inside cells. PARP inhibitor drugs work by blocking the PARP proteins from working properly, which means that the cells are unable to repair damaged DNA. This in turn often leads to the death of the cancer cells. PARP inhibitors specifically target

cancer cells, so that healthy cells are unaffected and the risk of difficult side effects is reduced. PARP inhibitors were first developed as a cancer treatment following research done in 2015 by a group of scientists in London. They were the first group to show that cancer cells with BRCA1/BRAC2 gene mutations were very sensitive to treatment with this class of drugs.

PARP INHIBITORS AND IMMUNOTHERAPY

Some tumors have defective DNA repair system, which turns on the body's alarm to send in immune cells because these tumor cells are seen as "foreign". To counteract this, some tumors avoid attack by the immune system by producing an increased amount of programmed cell death-1 with ligand (PD-L1), which is a molecule that disables the immune system's ability to launch an attack against cancer. This way, the tumor cell is able to hide from the immune system, making immunotherapy ineffective at killing the cancer cells. An example of an immunotherapy drug is Tecentriq (atezolizumab), which is a PD-L1 inhibitor. In March 2019, it was approved by the FDA to be used in combination with chemotherapy for the treatment of triple-negative, metastatic breast cancer in patients whose tumors ex-





press the PD-L1 protein.

Researchers have observed that combined treatment with a PARP inhibitor and a PD-L1 inhibitor is more effective at killing cancer cells than treatment with only immunotherapy. One theory is that the PARP inhibitor makes the tumor cell unable to repair the damaged DNA, and when the tumor cell produces increased amount of PD-L1 to avoid being attacked by immune cells, the PD-L1 inhibitor is able to easily target the cancer cells, which leads to death of the cancer cells.

PARP INHIBITORS AS TREATMENT FOR BREAST CANCER WITH BRCA GENE MUTATIONS

Breast cancers with BRCA gene mutations can be treated with PARP inhibitors. PARP inhibitors work by blocking the PARP proteins, which normally help repair damaged DNA inside cells. Cancer cells with a mutated BRCA gene already have trouble repairing damaged DNA, and these tumor cells tend to have very active PARP. The higher level of PARP activity in tumor cells compared to healthy cells makes it easy for the PARP inhibitor to target the tumor cells. Blocking the PARP proteins often leads to the death of the cancer cells.

- **Lynparza (olaparib) is a PARP** inhibitor that is used to treat patients who have been previously treated with chemotherapy and have an inherited BRCA gene mutation and have HER2-negative metastatic breast cancer.
- **Talzenna (talazoparib) is a PARP**

inhibitor that is used to treat patients who have an inherited BRCA gene mutation and have HER2-negative locally advanced or metastatic breast cancer.



PATIENT SUPPORT RESOURCES

- **Education & Advocacy:** Tigerlily Foundation provides education, advocacy, empowerment and support for young women under age 45, before, during and after breast cancer. See more information on our website (<http://tigerlilyfoundation.org>) or call 888-580-6253.
- **Financial Assistance:** Myriad recognizes that you and your families use genetic test results to make lifesaving medical decisions. Therefore, they promise to pro-



vide affordable access to testing, a lifetime commitment to accurate results and comprehensive support for all appropriate patients and their families. If you encounter any financial hardship associated with your bill or insurance, Myriad will work directly with you to resolve the matter: 844-MYRIAD9 (844-697-4239) or billing@myriad.com.

For qualified underinsured patients in the U.S., Myriad offers financial assistance to reduce out-of-pocket costs depending on your household income level. Examples of patients who are considered underinsured include:

- **Those with a high deductible** or out-of-pocket expenses
- **Those with a restrictive** medical policy

To be eligible, patients must have private insurance, meet the medical criteria for testing (see the link below), and meet low-income requirements (household incomes up to 400% of the Federal poverty level).

For qualified patients in the U.S. who do not have medical health insurance, Myriad offers financial assistance to reduce out-of-pocket costs depending on your household income level. To be eligible, patients must meet the medical criteria for testing, and meet low-income requirements (household incomes up to 400% of the Federal poverty level). Due to regulatory limitations, patients who are recipients of government-funded programs (e.g., Medicaid, Medicare, Medicare-Advan-

tage, and Tricare) are not eligible to apply for Myriad's Financial Assistance Program.

- **Genetic Counseling:** Genetic counselors are specially trained health professionals who help families learn about and cope with genetic conditions. If you are considering testing, a genetic counselor would discuss risks, benefits, and limitations and provide balanced information for you to make an informed decision about whether to proceed with testing. There are many issues to consider including psychological impact, family issues, and privacy. Genetic counseling can be helpful in addressing these issues. Genetic counselors support families and individuals in making decisions about genetic testing and in adjusting to test results. For more information on genetic counseling, visit the National Cancer Institute's website (<https://www.cancer.gov/about-cancer/causes-prevention/genetics/genetic-testing-fact-sheet>) or call 1-800-4-CANCER. To find a genetic counselor, you may visit the National Society of Genetic Counselor's website (<https://www.nsgc.org/>).

Myriad also offers genetic counseling. Call 844-MYRIAD9 (844-697-4239).

- **Support Groups:** If you have BRCA1/2 gene mutations or other gene mutation that increase your risk for breast cancer, you may benefit from joining a support

group. There are also support groups for people with BRCA1/2 gene mutations who do not have

cancer, and support groups for people with BRCA1/2 gene mutations who have cancer.



GLOSSARY

Biomarker: A biomarker or molecular marker is a biological molecule found in blood, other body fluids or tissues.

Biopsy: Biopsy is the examination of tissue removed from a living body. For example, a biopsy of breast cancer is taken to examine the characteristics of the tumor.

Clinical trial: A clinical trial is a type of medical research study that determines whether an intervention – a new drug, medical device or diagnostic tool – is safe and/or effective.

Companion Diagnostic: A companion diagnostic is a test or measurement that can be used to determine the efficacy and/or safety of a specific drug for a targeted patient group or patient sub-groups.

DNA: Deoxyribonucleic acid or DNA is a cellular component that contains the instructions for most forms of life.

Epigenomics: Epigenomics takes into account how factors, such as the environment, can result in changes in gene expression.

Gene Mutation: This is permanent change in the DNA sequence that makes up a gene. Gene mutations may be inherited from a parent or acquired during a person's lifetime.

Gene testing: Genetic testing is performed with a laboratory test to identify genetic changes associated with a disease.

Genetic Counseling: A healthcare professional with specialized knowledge of genetics meets with an individual or family to determine if a condition in the family is genetic and estimate the chances that another relative may be affected. Genetic counseling may also involve performing and interpreting genetic tests that estimate disease risk, as well as conveying information so as to help address concerns of the individual or family and provide psychological counseling to help them adapt to the condition or risk.

Genetic Marker: A genetic marker is an alternation in DNA that may indicate an increased risk of developing breast cancer.

Genome: The genome is the complete genetic material of an organism.

Genomic Sequencing: Genomic Sequencing is a method to determine the entire genetic makeup of a single cell or of an entire organism. This method can help determine changes in DNA that may lead to the development of breast cancer.



Genomics: Genomics is the study of the genome – structure, function, evolution and mapping.

GINA: The Genetic Information Nondiscrimination Act or GINA is a federal legislation that prohibits discrimination against individuals on the basis of their genetic profiles in regard to health insurance and employment. The law was passed in 2008.

Personalized medicine: This refers to treatment that is tailored to an individual patient, so that the patient is treated in the most effective manner. Diagnostic tools are used to identify specific biological markers to help determine which medical treatments and procedures will be best for the patient.

Pharmacogenomics: Pharmacogenomics is the field that examines how your genes influence the way your body processes medications used to treat breast cancer.

Proteomics: Proteomics is the analysis of protein structure and function.

Risk factors: A risk factor is a characteristic or exposure of an individual that increases their likelihood of developing breast cancer.

Targeted therapy: Targeted therapy is drugs for breast cancer that are designed to attack certain cancer cells or certain cellular pathways that cancer cells use to grow and survive.

Tumor sequencing: Doctors can sequence the DNA from your cancer cells to identify which mutations are responsible for causing breast cancer.

NOTES

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